REMARKS/ARGUMENTS

I. Status of the Claims and Amendments:

Claims 100 –143 have been cancelled for brevity and in light of previously added new claims. Although the prior office action recited pending claims up to number 197, it appears that claim 192 is the highest number of the pending claims. Thus claims 144 – 192 are considered to be pending in the application. Support for the amendment to claim 144 reciting alternations that reverse a ligand specificity of the receptor and confer activation by the antagonist can be found for example on page 27, line 2. In the course of preparing the present correction to the amendments in accordance with the notice of non-compliance, it was noticed that there was an obvious error in pending claim 184, which recited "Org 3186." With the Examiner's permission, entry of an amendment at this time is respectfully requested to correct this typographic error to "Org31806" as per the specification on page 10, line 20. If such correction cannot be made at this time, Applicant will provide a correction by amendment at a later time.

II. Rejections under 35 U.S.C. § 101

The Examiner has rejected claims on the basis of 35 USC 101 citing the PTO's position outlined in 1077 OG 24. It is the Applicant's belief that 1077 OG 24 stands for the proposition that applications would be accepted claiming non-naturally occurring nonhuman multicellular living organisms, including animals, but thus establishing that claims to humans would not be permitted. The present application does not claim animals, human or otherwise but instead presents method claims for regulating gene expression. As such, the present claims in the human context are analogous to methods of treatment using administration of drugs for intended therapeutic benefit. The method is applicable to regulating expression in animals, including humans, into which a nucleic acid encoding a ligand inducible molecular switch has been introduced for transient expression and to transgenic non-human animals expressing the molecular switch. Expression from the nucleic acid thus resident in the animal, whether transient if administered or endogenous if transgenic, is activated by ligand administration to induce expression of desired target genes.

Although not acquiescing to the relevance of the present rejection to the previously pending method claims, for purposes of advancing prosecution in light of the Examiner's 35 USC 101 concerns, the independent claims have been amended as follows. Independent 144, and thus the claims dependant therefrom, has been amended to include a limitation to non-human animals. Independent claim 168, and thus the claims dependant therefrom, has been amended to clarify that the molecular switch expression cassette has been previously administered to an animal for transient expression or is comprised in a non-human transgenic animal. Where the expression cassette has been previously administered to an animal,

including humans, for transient expression, this means that the genetic material encoding the molecular switch is designed not to be integrated into the host cell genome or replicated and is accordingly eliminated from the cell over a period of time. *See the definition of "transient" in the written description on page 13, lines 13 – 17.* Similarly, independent claim 177, and thus the claims that depend therefrom, recites a method of regulating transient expression wherein the animal has been previously administered the nucleic acid encoding the molecular switch. Thus, the claims have been amended to clarify that the animals, including humans, are administered the nucleic acid for transient expression. Germ-line transmission of nucleic acids encoding the molecular switch thus resulting in a "transgenic human" is not claimed.

III. Rejections under 35 U.S.C. §112

The Examiner, while conceding that the specification is enabling for certain transgenic applications, appears find that the specification is not enabling for other transgenic applications or long term expression. The method of the present invention has in fact been readily adopted by those of skill in the art of transgenics for its particular value in regulating the temporal expression of any given gene product in transgenic animals upon administration of the ligand. For this reason, the present invention has been particularly valuable in transgenics where it permits the study of genes whose expression would be lethal during development. For example, included herewith is an article by certain of the present inventors detailing the application of the claimed invention to transgenic mice for regulated expression in which the transgene was readily induced by ligand administration in vivo. *See Wang et al. Nature Biotechnology 15 (1997) 239.* A review article by Bockamp et al, *Physiol Genomics* 11: 115 (2002), included herewith, reiterates the particular advantages of the steroid hormone molecular switch in transgenic applications. Numerous further examples of the effective use of the claimed method of ligand regulated expression of target genes utilizing the molecular switch of the present invention can be readily provided that fully demonstrate expression of the regulated transgene at levels sufficient for phenotypic expression. The details of transgenic animal generation at the time the applications was filed were well known in the art and were thus not necessary for understanding or using the claimed method of regulating target gene expression through administration of a ligand that activates a molecular switch specific for expression of the target gene promoter.

Regarding the Examiner's concern relating to "long term expression", in the case of transgenics, the molecular switch could be expected to be expressed constitutively or in a tissue specific manner for the life of the animal and its progeny. The presence of the target gene, whether endogenous or introduced into the germ-line of a transgenic could likewise be expected to persist indefinitely although expression of the target gene would only occur in the presence of administered ligand.

Where the nucleic acids have been administered to an animal using an expression vector, expression is expected to be "transient" in that the expression vector will eventually be lost to cell division. Nonetheless, "transient" expression can still be considered "long-term." As set out in the attached article by Nordstrom, *Steroids* 68 (2003) 1085-1094, pg. 1091, ligand inducible expression of target genes under the present method has been observed for at least a year following single administration of expression vectors encoding the molecular switch of the present invention.

The Examiner has argued that the specification is not enabling for the generation of any mutation in the ligand binding domain of any steroid hormone receptor. This rejection is respectfully traversed as it applies to pending claims 144 – 176. The present inventors taught that modification of amino acid sequence in the ligand binding domain of steroid hormone receptors could convert an antagonist of the naturally occurring receptor into an antagonist and that this mutated ligand binding domain could be combined with non-steroid hormone receptor DNA binding domains as well as heterologous transregulatory domains. The molecular switch thus produced could be utilized to regulate the expression of genes *in vivo* through the administration of a ligand to the animal that would not activate endogenous receptors. The present inventors demonstrated their invention with the progesterone receptor but also taught the generation of molecular switches based on other steroid hormone receptors including among others the estrogen receptor and glucocorticoid receptor.

Others readily appreciated the power of this discovery and have subsequently demonstrated the validity of this teaching in the generation of molecular switches based on the other steroid hormones taught by the present inventors including the estrogen and glucocorticoid receptors. The basis of these demonstrations in the teachings of the present inventors was cited in Brachen et al, US Application 10/157,899, published as US2003/0143559, describing the generation of a molecular switch including heterologous DNA binding and transactivation domains together with mutated estrogen receptor ligand binding domains result in activation by antiestrogens.

Glucocorticoid receptor mutants have been generated based on the seminal teachings of the present inventors. See, for example, Lanz et al *Endocrinology* 135 (1994) 2183 (already of record but a copy of submitted here for the convenience of the Examiner). The teachings of the present invention have enabled others of skill in the art to generate mutated steroid hormone receptors that are "inverted" with respect to ligand activation, thus enabling the generation of molecular switches that are not activated by endogenous ligands.

Claims 177 – 192 relate to a specific embodiment in which the steroid hormone receptor is a progesterone receptor having an alternation in one or more of the C-terminal 54 amino acids. These claims have been amended to claim administration for transient expression. Specific examples of both 54 and 42

amino acid deletions were provided in the specification at, for example, page 29, lines 10 – 30. Given this teaching, undue experimentation would not be required to identify further deletions or substitutions in this region that would provide the same result as the surprising discovery of the present inventors that modification of amino acid sequence in this region would convert an antagonist of the naturally occurring receptor into an antagonist.

Amendments to claims 152 and 182 are made to correct errors in the recitation of the chemical formula, consistent with the specification and prior corrections thereto. Minor corrections to certain of the claims have been made for purposes of grammar and to clarify dependencies.

Conclusion

For the reasons stated herein, the Applicant respectfully submits that independent claims 144, 168 and 177 are allowable and that the dependent claims are, in turn, also allowable. Applicant respectfully requests allowance of the claims at an early date. The Commissioner is authorized to charge any additional fees incurred in this application or credit any overpayment to Deposit Account No. 50-1922. Should the Examiner have any questions, please do not hesitate to call Applicant's attorney at 832-446-2421.

Respectfully submitted,

By _____

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